ASSOCIATION BETWEEN GENETIC POLYMORPHISM AND LUNG CANCER: A COMPREHENSIVE REVIEW

By

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons.)

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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The thesis titled "Association between genetic polymorphism and lung cancer: A comprehensive review" submitted by Tamima Lorna (21146044), of Spring, 2025 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

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Ethics Statement

This study did not involve any human participants, human specimens or tissue, vertebrate animals or cephalopods, vertebrate embryos or tissues and field research.

Abstract

Lung cancer is a complex multifactorial disease which is influenced by both genetic predisposition and environmental factors. Various single nucleotide polymorphisms in DNA repair genes (BRCA2, RAD52, ERCC1, XRCC1), tumor suppressor gene (TP63), detoxifying genes (CYP2A6, GSTM1, GSTT1), nicotinic dependence gene (CHRNA5), drug transport genes (ABCB, ABCG2), immune system regulatory gene (PD-L1), influence the lung cancer risk, development and treatment response. The purpose of this research is to incorporate the existing studies regarding the association between genetic polymorphism and lung cancer susceptibility, focusing on some key genes, gene-environmental interactions, ethnic variability and pharmacogenomics, to understand the mechanism of the disease and to improve treatment outcomes. A systematic review of relevant existing studies was conducted and information was taken from credible sources such as Google Scholar, PubMed, ScienceDirect, EMBASE, Web of Science, Scopus. Overall findings suggest that single nucleotide polymorphisms alone might have minimal effect but integration with multiple pathways, for example, gene-environment interactions and ethnic variability significantly influences lung cancer susceptibility and responses to treatment. The study of the association between genetic polymorphism and lung cancer is important to understand as it has many contributions in the healthcare sector. Combining genetic profiles, environmental factors and clinical data helps in the management of lung cancer, which ultimately, leads to increased survival rate of patients. There are some limitations to these studies, hence future research should concentrate on conducting large multi ethnic studies, refine PRS models, gene-environment interactions, functionally validate SNPs and integrate genomic biomarkers into clinical practice.

Keywords: Polymorphism; Lung cancer; DNA repair genes, detoxifying gene, pharmacogenomics

Dedication

I would like to dedicate this project to Allah (SWT) for giving me knowledge, blessings and guidance, to my family whose unwavering support has given me strength, to my esteemed advisor, Dr. Md. Aminul Haque whose mentorship, guidance and invaluable belief in my abilities helped me in shaping this research and lastly, to myself for being persistent, determined, patience and diligent.

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List of Acronyms

ABCB1	ATP-binding cassette subfamily B member 1
ABCG2	ATP-binding cassette subfamily G member 2
ALK	Anaplastic Lymphoma Kinase
BER	Base Excision Repair
BRCA1	Breast Cancer gene 1
BRCA2	Breast Cancer gene 2
CHEK2	Checkpoint Kinase 2
CHRNA3	Cholinergic receptor, nicotinic, alpha 3
CHRNB4	Cholinergic receptor nicotinic beta 4 sub-unit
CHRNA5	Cholinergic receptor nicotinic alpha 5 sub-unit
CRISPR-Cas9	Clustered Regularly Interspaced Short Palindromic Repeats and CRISPR-associated protein
CYP1A1	Cytochrome P450 Family 1 Subfamily A Member 1
CYP2A6	Cytochrome P450 family 2 subfamily A member 6
CYP2E1	Cytochrome P450 family 2 subfamily E member 1
DNA	Deoxyribonucleic acid
DSBR	Double-strand break repair
EGFR	Epidermal Growth Factor Receptor
ERCC1	Excision repair cross-complementing rodent repair deficiency, complementation group 1,
ERCC2	Excision repair cross-complementing rodent repair deficiency, complementation group 2.
GSTM1	Glutathione S-transferase Mu 1,
GSTP1	Glutathione S-transferase Pi 1

GSTT1	Glutathione S-transferase Theta 1,
GWAS	Genome wide association studies
HIF-1α	Hypoxia-Inducible Factor 1, Alpha Subunit
HRR	Homologous Recombination Repair
KRAS	Kirsten rat sarcoma viral oncogene homolog
MMR	Mismatch Repair
NER	Nucleotide Excision Repair
NSCLC	Non-Small Cell Lung Cancer
OGG1	8-oxoguanine DNA glycosylase 1
PD-L1	Programmed Death Ligand 1
PRS	Polygenic Risk Score
RAD52	RAD52 Homolog, DNA repair protein.
RB1	Retinoblastoma susceptibility gene
SCLC	Small cell lung cancer
SNP	Single Nucleotide Polymorphism
TP53	Tumor protein p53
TP63	Tumor protein p63
XPA	Xeroderma pigmentosum, complementation group A
XPD	Xeroderma pigmentosum group D.
XRCC1	X-ray repair cross-complementing protein 1
XRCC3	X-ray repair cross-complementing group 3

Glossary

Term	Definition
Atelectasis	collapsing of part or all of a lung due to blockage of air passages or by pressure exerted on the lungs
Non-small cell lung cancer	a type of lung cancer characterized by cell origin and growth patterns
Small cell lung cancer	Fast growing tumor in the lung tissue that spread to other parts of the body, characterized by small and oval shape cancer cells
Adenocarcinoma	It is a subtype of NSCLC and is originated in the mucus secreting tissue of the lung
Squamous cell carcinoma	It is a subtype of NSCLC and originates from squamous cells, lining the airways
Large cell carcinoma	Aggressive form of the subtype NSCLC that appear in any part of the lung
Single nucleotide polymorphism	a common type of polymorphism that occurs in more than 1% of the population where a single nucleotide like A, G, C, T vary among individuals
Polymorphism	possessing multiple forms

Gene expression	a process where information encoded in the gene, is used to create functional product, particularly protein
Hypoxia	oxygen deficiency in body tissues
KRAS	a gene that encodes a protein called K-Ras (a part of RAS/MAPK signaling pathway)
Genetic Predisposition	increased chance of developing disease based on an individual genetic makeup
CHEK2 Checkpoint Kinase 2	a tumor suppressor gene that encodes a protein called CHK2 (involved in apoptosis, cell cycle regulation and response to DNA damage)
Biomarker	a biological molecule that is found in tissues, blood, body fluids by which certain physiological and pathological processes, diseases can be recognized
Genome wide association studies	a method that scans genome in individuals and compare their genome to find genetic markers that are linked with a disease or trait

Chapter 1

Introduction

1.1 Background and Significance

What is lung cancer and its etiology

Lung cancer is a type of cancer where abnormal cells in the lungs grow uncontrollably and form a malignant tumor which interferes with the normal cell function. It is also known as lung carcinoma. These lung tumors can break open and spread to other parts of the body, a process known as metastasis. Impaired lung function leads to shortness of breath where tumors block the airways lining, leading to difficulty in breathing. Other impaired functions lead to chronic cough, wheezing, atelectasis (lung collapse) further reducing lung capacity. There are several risk factors that can contribute to the occurrence of lung cancer such as tobacco smoking which is the leading cause and is responsible for approximately 85% of all lung cancer cases depending on the increasing duration and amount of tobacco smoked. Other includes radon exposure (which is radioactive gas occurring naturally and is the second most common cause of lung cancers in non-smokers), exposure to chemicals (such as carcinogens, arsenic, asbestos, diesel exhaust increase the risk significantly), exposure to long term air pollution (also significantly increases the risk of lung cancer), chronic obstructive pulmonary disease (are linked to higher risk of lung cancer), previous radiation therapy on the chest (also increases the risk), dietary factors (which includes low consumption of fruits and vegetable and poor diet are linked to increased lung cancer risk), infections such as tuberculosis and other chronic respiratory infections (may increase the risk of lung cancer). Generally, predisposition and family history also play a role in increasing lung cancer risk.

Overview of lung cancer statistics:

According to the world health organization, lung cancer is the most commonly diagnosed cancer worldwide with 2.5 million new cases reported in 2022, which accounts for a 12.5% among all new cancer cases. Amongst the cancer related deaths, lung cancer is the most leading cause, with 1.8 million mortality rates, constituting 18.7% of total cancer deaths globally. These numbers highlight how deadly lung cancer is and the importance of preventing the disease and the development of treatment strategies. Smoking is the major cause of lung cancer but it has also been observed that the number of cases also increased in non-smokers with approximately 15% of lung cancer patients who never smoked, accounting seventh leading cause of lung cancer death in non-smokers among solid tumors. It has also been seen that lung cancers in non-smokers were mainly women and this highest incidence is found in South East Asia (Torok et al.,2011). Various factors play role in the development of lung cancer but genetic factors also play a role in lung cancer in non-smokers which highlight the need for further research for prevention, early diagnosis and novel therapeutic targets to deal with this growing public health matter (Torok et al.,2011).

Types of lung cancer

Lung cancer is mainly classified into two main categories. They are, non-small cell lung cancer (NSCLC)and small cell lung cancer (SCLC). Among them, 85.4% of cases accounts for NSCLC and 14.6% represents SCLC (Mohan et al.,2016). NSCLC has subtypes. They are squamous cell carcinoma (30%), adenocarcinoma (28.3%) and large cell carcinoma (1.7%) (Mohan et al.,2016) and these three subtypes are the main histopathological groups (Bonastre et al.,2016).

Non-small cell lung cancer is the most common type of lung cancer. It has subtypes and is characterized by cell origin and growth patterns.

Adenocarcinoma- It is a subtype of NSCLC and is originated in the mucus secreting glands and can be found in the outer regions of the lung. In non-smokers it is most common and tend to grow slowly compared to other types

Squamous cell carcinoma-It originates in the squamous cells which line the airways. It develops in the central part of the lung and is associated with smoking

Large cell carcinoma- It is characterized by large abnormal looking cells and is a more aggressive form of NSCLC and appears in any part of the lung.

NSCLC is linked with various genetic factors which includes mutations in the epidermal growth factor receptor (EGFR) and rearrangements of the anaplastic lymphoma Kinase (ALK), which drive tumor growth and can influence the treatment response. On the other hand, small cell lung cancer is less common and is characterized by small oval shaped cells which multiply rapidly and form large tumors. They form clusters and are mainly two types: one that remains in one lung and nearby lymph nodes and the other types spread beyond the origin of tumor growth. It is associated with smoking and usually spreads rapidly to other parts of the body. SCLC is often associated with genetic mutations such as RB1 and TP53(critical for cell cycle regulation). Therefore, these both types of lung cancer are different in characteristics, risk factors and have different treatment approaches and so, understanding these differences helps to manage and diagnose effectively.

Genetic Polymorphisms and its correlation with lung cancer:

Genetic polymorphisms refer to the incident of two or more versions of the same gene that takes place within a population, with a prevalence of at least 1% of the least frequent allele.

These genetic variants can exist in different forms such as single nucleotide polymorphisms (SNPs) where a single nucleotide is substituted instead of another nucleotide, deletions or insertions of DNA sequences. These variations in genes lead to differences in gene expression, protein function and may also increase susceptibility to diseases such as cancer. As a part of lung cancer, polymorphisms in genes which are involved in DNA repair pathways (such as, ERCC1, XPD), metabolic pathways (such as, GSTP1, CYP1A1), and hypoxia response (such as, HIF-1 alpha) have been widely studied. For example: The gene ERCC1 which is involved in nucleotide excision repair (NER), polymorphisms in this gene are associated with altered capacity of DNA repair and lead to increased lung cancer risk (Zheng et al.,2017). Likewise, polymorphisms in CYP1A1 gene which plays a role in the metabolism of tobacco carcinogens and is associated with the lung cancer risk, especially in smokers (Song et al.,2001).

Importance of understanding genetic susceptibility in lung cancer development

Understanding genetic predisposition in the development of lung cancer is important for several reasons as genetic factors play a crucial role in determining an individual's lung cancer risk, particularly in non-smokers or light smokers and determining these factors helps in detection, screening, prevention, diagnosis and treatment strategies in lung cancer.

Polymorphisms in genes such as KRAS, TP53, EGFR are associated with increased risk of lung cancer (Hsiung et al.,2010; Mckay et al.,2017). If these genes are detected early through genetic screening, then chances of survival rate could be increased (National Cancer Institute, 2021). Individuals with genetic susceptibility to lung cancer can reduce the risk by modifying their lifestyle, such as, smoking cessation, avoiding harmful environments, carcinogens and regular screening. Studies suggested that genetic predisposition interacts with environmental factors such as tobacco smoke, further increasing the risk of cancer (Amos et al.,2008). Thus,

if high risk individuals are identified, then preventive measures could be easily taken. Hereditary factors, also increases susceptibility to lung cancer and germline mutations in genes, such as, CHEK2, BRCA1, BRCA2, increases lung cancer risk, especially in people, where their multiple family members are affected by lung cancer (Bailey-Wilson et al.,2004). Therefore, understanding the hereditary risk factors, can help individuals in genetic counselling and screening programs. Individualized treatment approaches could be done if potential biomarkers for genetic susceptibility are identified, which lead to improvement in efficacy and reduce adverse effects (Herbst et al.,2018). Example include, mutations in the EGFR gene respond to EGFR tyrosine kinase inhibitors in non-small cell lung cancer (Lynch et al., 2004).

1.2 Objective of the Study

Aim of this review is to analyze and integrate the research on the effect of genetic polymorphisms in lung cancer predisposition, advancement and treatment response. In this study, the focus will be on some key genes that are involved in repairing DNA, suppressing tumor growth, detoxifying harmful substances and metabolism of drugs.

Chapter 2

Methodology

2.1 Methods and materials

A systematic review of relevant existing studies on the association between genetic polymorphism and lung cancer was conducted. This review focuses on candidate genes that might be linked with lung cancer risk, its progression and treatment outcomes. The literature review was conducted from multiple scientific databases which include, Google Scholar, PubMed, EMBASE, ScienceDirect, Scopus, Web of Science. The search term was used by combining medical subject headings and keywords such as, 'Association between genetic polymorphism and lung cancer',' DNA repair genes and lung cancer', 'Genetic variants in lung cancer risk', 'lung cancer statistics',' Combined effect of genetic polymorphism',' gene-environment interactions and its association with lung cancer',' detoxifying genes polymorphisms and its association with lung cancer risk, 'pharmacogenomics related to lung cancer'. To make the research relevant to the topic, articles were selected based on some inclusion criteria such as studies focusing genetic polymorphisms that are linked with lung cancer, genome wide association studies (GWAS), gene-environment interactions that are associated with lung cancer risk, pharmacogenomics and treatment outcomes in lung cancer. Exclusion criteria included studies that focused on other cancers, studies found no association, studies with low stability power. The study analyzed some key genes and their mechanisms, explaining how they can contribute to lung cancer risk.

Chapter 3

Discussion

3.1 Genetic Variations in DNA repair genes

DNA repair genes play a key role in repairing damaged DNA through several pathways such as base excision repair (BER), mismatch repair (MMR), nucleotide excision repair (NER), and Double-strand break repair (DSBR) (Liu et al.,2019). This repair system is important for preventing mutations in DNA, thus maintaining cellular health and ultimately preventing development of various diseases including cancer. Genetic variations in DNA repair genes are linked with an increased risk of lung cancer such as polymorphisms in base excision repair gene and nucleotide excision repair (NER) genes which include XPA, OGG1, and ERCC2 are linked with altered lung cancer risk (Kiyohara et al.,2010). In DNA repair genes several polymorphisms are associated with lung cancer risk. They are:

- The BRCA2 gene plays a key role in homologous recombination repair (HRR), which is a mechanism that repairs double-strand breaks in DNA, thus restoring genetic information accurately without introducing mutations (Scully et al.,2019). Mutations in BRCA2 gene could lead to genetic instability and increased risk of cancer (Lord and Ashworth,2016). The polymorphism rs11571833 is particularly responsible for introducing a premature stop codon, which results in non-functional BRCA2 protein (Momozawa et al.,2018). As a result, the dysfunctional gene unable to repair double strand breaks repair and accumulation of unrepaired DNA breaks leading to cancer development (Medici et al.,2020). It has been found that mutations in BRCA2 are associated with increased susceptibility to lung cancer, especially among non-smokers and people with a family history of cancer (Wang et al.,2019).

- RAD52 gene also plays a key role in homologous recombination repair where they help in rejoining the single stranded DNA ends and variations in this gene are associated with lung cancer susceptibility, especially in lung squamous cell carcinoma (Hua et al.,2016). The rs7963551 (which is a specific single nucleotide polymorphism in RAD52) affects the expression of RAD52 gene and determines how much RAD52 protein will be produced. This polymorphism reduces RAD52 gene expression and so DNA repair becomes less efficient, ultimately leading to accumulation of damaged DNA, promoting lung squamous cell carcinoma. On the other hand, amplification of RAD52 in cancer cells, helps the tumor cells to survive, thus making the cancer more aggressive. In one analysis, reducing the RAD52 in mouse lung tumor cells caused DNA damage and tumor cell death. Therefore, mutation in RAD52 or overexpression could influence the development of lung cancer and its progression.

- Tumor suppressor genes such as TP63 plays a role in the regulation of cell cycle progression and cell apoptosis (Wang et al., 2013). Polymorphism rs10937405 in the TP63 gene has been associated with increased risk of lung cancer, especially in the East Asian population. In a study, it has been found that rs10937405-G allele was associated with lung adenocarcinoma, especially in never-smoker Asian females (Shiraishi et al.,2012). Variations in rs10937405 also influence other gene expression which enhances the risk of non-small cell lung cancer, particularly in North Indian populations (Rai et al.,2019).

3.2 Ethnic variability and lung cancer susceptibility

Genetic polymorphisms also depend on ethnicity which influence vulnerability and progression of lung cancer. Genetic polymorphisms in the KRAS, TP53 and EGFR gene show varying effects among different ethnic groups. Examples include, mutations in EGFR gene are mainly

carried by East Asian populations and this mutation is associated with increased risk of lung adenocarcinoma (Shirashi et al.,2012). On the other hand, Caucasians carry a higher frequency of mutated KRAS genes which are associated with more aggressive lung cancer (Zhao et al.,2019). Furthermore, genetic polymorphism in CYP2A6 gene showed different levels of risk in lung cancer among different ethnicities (Zhou et al.,2018). Therefore, consideration of ethnic variability is important in assessing lung cancer susceptibility and also in personalized medicine.

3.3 Detoxifying enzyme role in lung cancer susceptibility

Detoxifying enzymes play an important role in protecting the body from harmful substances such as carcinogens in tobacco smoke and environment pollutants. These enzymes metabolize and neutralize harmful chemicals, thus reducing DNA damage and cancer development. Cytochrome P450 enzymes are the key enzymes which are involved in detoxification and their subtypes are CYP1A1, CYP2A6 and CYP2E1. These enzymes metabolize specific tobacco carcinogens such as polycyclic aromatic hydrocarbons and nitrosamines (Martinez et al.,2020). Genetic Variations in these detoxifying genes may lead to increased or decreased rate of clearance of harmful substances from cells. CYP2A6 gene encodes an enzyme that is involved in metabolizing nicotine and also activates specific tobacco carcinogens such as nitrosamines (Zhou et al.,2018). Polymorphism rs1801272 in CYP2A6 gene reduces the activity of this enzyme, thus affecting the metabolism of nicotine (Abdel Rahman et al.,2018). On the other hand, a study which is conducted in the Egyptian population showed that there is no significant association between rs1801272 and lung cancer risk (Abdel Rahman et al.,2018). In fact, in smokers, higher amounts of CYP2A6 are linked with greater risk of lung cancer because higher metabolism leads to consumption of more cigarettes, resulting in higher amounts of carcinogen exposure (Bloom et al.,2023). Though, rs18011272 polymorphism decreases the activity of

CYP2A6 enzymes, recent research does not suggest a direct link between lung cancer susceptibility with this variant (Zhou et al.,2018).

3.4 Interactions of Gene-Environment in lung cancer susceptibility: Smoking and its association with lung cancer

We already know, smoking is the greatest contributor and accounts for 85% lung cancer cases worldwide (Siegel et al.,2023). Tobacco smoke contains carcinogens such as formaldehyde, nitrosamines and benzopyrene and can damage the DNA, causing mutations in the lung cells (Hecht,2012). Extreme exposure to these chemicals in the body leads to oxidative stress, inflammation and uncontrolled cell growth, causing increased risk of cancer (Yuan et al.,2020). Furthermore, variations in genes that play a key role in detoxifying harmful substances and repairing DNA damage, for example, CHRNA5, can make an individual susceptible to smoking-related lung cancer (Bosse et al.,2012).

- CHRNA5 is a gene that encodes an alpha 5 subunit of nicotinic acetylcholine receptors. This receptor is responsible for sending nerve signals when nicotine binds with them. Some of these nerve signals cause nausea and dizziness, therefore it causes individuals to feel negative effects of smoking. Variations in this gene such as rs16969969(which is a single nucleotide polymorphism) causes an amino acid substitution at position 398 which causes changes from aspartic acid to asparagine, as a result receptor function reduces (Ware et al.,2011). Therefore, people with this mutation(rs16969969) are less likely to feel the negative effects of smoking and they tend to smoke more, as their body does not warn them to stop smoking (Benowitz,2010). Increased smoking results in greater exposure to carcinogens and damaged DNA which increases the risk of developing lung cancer (Saccone et al.,2010). Moreover, this receptor is also found in the lungs where they regulate cell proliferation and apoptosis (Ware et al.,2011). If this

receptor becomes dysfunctional due to polymorphism rs16969968, then they promote cell growth in the lungs, further causing the risk of developing cancer (Benowitz,2010).

Genetic Susceptibility and waterpipe Smoking

Waterpipe smoking contains more carcinogens compared to normal cigarette smoke and it has more popularity in Middle Eastern countries. This has raised public health concern especially between its association with lung cancer. In a recent study, the polymorphisms GSTM1, GSTT1 and GSTP1 which play a role in the detoxification of harmful substances have been examined between its association with lung cancer risk among male Iraqi water pipe smokers. In this study, it has been found that, individuals with inactive GSTM1 exhibit a significant risk of developing lung cancer when it is combined with water pipe smoking and GSTT1 genotype effects has a three-fold increased risk of developing lung cancer. On the other hand, GSTP1 polymorphisms do not show any significant association with lung cancer risk. This study highlights the complex interplay between environmental carcinogens with genetic susceptibility which is related to lung cancer risk among the Iraqi male smokers. This study also suggests that genetic polymorphism could contribute to the risk of developing lung cancer when the individual is exposed to certain carcinogens, such as waterpipe smoking.

3.5 Genetic polymorphisms in DNA repair genes and chemotherapy response

Platinum-based chemotherapy is often the first line treatment for lung cancer. But a major problem lies in chemotherapy treatment is the chemoresistance which greatly reduces treatment efficiency. Growing evidence suggests that genetic polymorphism affects an individual response to chemotherapy by modifying the DNA repair, metabolism, drug transport mechanisms and also immune system interactions (Sito and Tan,2024).

Therefore, understanding these genetic polymorphisms can help in the selection of proper chemotherapy treatment which ultimately enhance personalized treatment strategies. Platinum-based chemotherapy such as carboplatin and cisplatin react with DNA and form DNA adducts, thus damaging the DNA and causing cell death. But some cancer cells survive this damage by using DNA repair mechanism, especially using nucleotide excision repair pathway, where they play an important role in repairing the damaged DNA, which is caused by platinum-based chemotherapy.

ERCC1 is a gene that plays a key role in the nucleotide excision repair pathway, where it fixes the damaged DNA caused by platinum-based chemotherapy. Polymorphism in ERCC1 such as rs11615 (C>T) and rs3212986(A>G) are linked with chemotherapy resistance and patients with this variant are able to repair damaged DNA, allowing the cancer cells to survive. On the other hand, ERCC2 is another nucleotide excision repair gene, which reduces DNA repair activity, thus making cancer cells more vulnerable to platinum drugs (Sito and Tan,2024).

XRCC1 is a gene that is involved in base excision repair pathway, where they repair single stranded break DNA caused by chemotherapy. Individuals with XRCC1 rs25487 polymorphism reduced ability in repairing damaged DNA. This means that individuals could either develop sensitivity to chemotherapy, as DNA repair is less efficient or they might develop chemoresistance as some cancer cells might use other pathways to survive, depending on the patient's genetics and the type of cancer (Sito and Tan,2024). Another gene XRCC3 which is involved in homologous recombination repair and their polymorphism rs861539 have been associated with chemotherapy sensitivity (Sito and Tan,2024).

3.6 Genetic polymorphisms and its effect on drug transport, metabolism and immune response mechanism in chemoresistance and chemotherapy sensitivity

Drug transporters such as ATP binding cassette transporters are involved in the regulation of uptake and efflux of drugs, including platinum drugs. Genes such as ABCB1 and ABCG2 are involved in encoding efflux transporters, which pumps drugs out of the cell. Polymorphisms ABCB1 rs1045642 and ABCG2 rs2231142 are associated with chemoresistance, as the transporter effectively pumps drugs out of the cell, thus reducing platinum drugs inside the tumor cells. Therefore, these variants result in poor chemotherapy response and reduce transport efficiency (Sito and Tan,2024).

The GSTP1 gene is involved in metabolism and detoxifying chemical substances, including platinum drugs. But GSTP1 rs1695 polymorphism reduces the activity of enzymes, as a result more chemotherapy drugs remain inside the cell, leading to better response (Sito and Tan,2024).

Immune system interactions and tumor microenvironment also contribute to chemoresistance. Variation in genes that regulate immune checkpoint and inflammation could affect chemotherapy treatment. Programmed death ligand 1 (PD-L1) gene plays a role in suppressing immune cell activity in tumor cells. Polymorphisms in PD-L1 gene such as rs2297136 and rs4143815 are linked with increased expression of PD-L1 gene, therefore, helping the tumor cells to overcome from immune cell attack, leading to chemoresistance (Sito and Tan,2024).

Chapter 4

Challenges, Future prospects and clinical implications

4.1 Limitations regarding genomic studies associated with lung cancer

Genetic studies have identified different single nucleotide polymorphisms that have been associated with lung cancer risk. Genetic association studies have faced multiple challenges such as ethnic variability, statistical limitations, small sample size, gene environment interactions and lack of replication and reliability. Therefore, these challenges should be addressed as it is important to translate genetic findings into clinical applications. One of the major challenges is the genetic heterogeneity among different ethnic groups. This means that people have different genetic makeup across different populations such as Europeans, Africans, Asians. Genomic data are more available on European populations and single nucleotide polymorphism in European populations may not match with other ethnic groups such as Asians or Caucasians because of different allele frequencies and linkage disequilibrium (Amos et al.,2020). As a result, genes which are associated with lung cancer risk for European populations may not function in the same way for African or Asian populations. Therefore, it becomes more difficult to generalize the association between genetic polymorphism and lung cancer across different ethnic groups. One of the examples include epidermal growth factor receptor mutations which are associated with lung adenocarcinoma, more commonly in non-smokers Asian females compared to Caucasian populations. This means that genes which are associated with lung cancer risk in Europeans may not predict the risk in Asians (Zhao et al.,2019). Hence, this issue should be considered, as EGFR inhibitors are more effective in the Asian population compared to Caucasians.

Polygenic risk Score (PRS) is a tool that is used to predict lung cancer risk among the population by combining the effect of multiple single nucleotide polymorphisms. Higher PRS

score is associated with higher risk of developing lung cancer and lower score refers to low risk. This PRS also has limitations such as inconsistent single nucleotide polymorphism where they combine different ethnic groups SNPs, thus making it harder to develop a standard polygenic risk score that can be used for everyone (Amos et al.,2020). Another limitation of PRS is that it is less accurate for non-Europeans as their genetic makeup is different compared to Europeans and most of the PRS model is developed from the European population using large datasets and leads to less accurate estimation (Amos et al.,2020). Lastly, PRS is less accurate in predicting lung cancer risk because it does not consider external factors such as smoking, air pollution, lifestyle factors, chemical exposure such as asbestos and these factors greatly influences lung cancer risk along with the genetic factors. Therefore, to accurately predict lung cancer risk, the PRS model should integrate both clinical and environmental factors that are associated with lung cancer risk (Amos et al.,2020).

Small sample size is another limitation, as it contributes to low statistical power and may give false positive results, making the genomic studies less accurate (Wang et al.,2021). Genome wide association studies on large scale to detect rare variants requires thousands of participants but many studies utilize a limited amount of population which makes the studies less reliable (Houlston et al.,2020).

Lung cancer risk is influenced by both genetic and environmental factors but many genetic associated studies do not consider the environmental factors, leading to inaccurate predictions about lung cancer risk. Single nucleotide polymorphisms such as CHRNA3, CHRNA5, CHRNB4 which are linked with nicotine dependence and they might have greater influence in smokers compared to non-smokers but these combined relationship between genetic and environment are often not analyzed properly (Saccone et al.,2019).

Genetic association studies must be able to replicate in independent studies, i.e. it must show the same result in multiple independent studies, only then it can be considered as a reliable genetic risk factor for lung cancer but many studies fail to replicate which raises questions about their reliability. (Houlston et al.,2020). This occurs due to differences in data collection method, different statistical approaches and differences in study design i.e. some study uses case-control design while other uses cohort studies, as a result all these differences lead to inconsistent results (Houlston et al.,2020). Moreover, variations in sample population such as genetic variations in ethnic groups differ from each other, therefore SNP in one ethnic group that is linked with lung cancer may not be relevant to another ethnic group and so the SNP may not be a universal risk factor. Furthermore, small population size also contributes to statistical error which leads to false positive results which cannot be made sure in larger studies (Wang et al.,2021).

Differences in genotyping methods i.e. detecting single nucleotide polymorphism and differences in statistical methods also produce contradictory results.

4.2 Future directions of association between genetic polymorphism and lung cancer

Lung cancer is one of the most complex genetic malignancies and is influenced by various factors such as ethnic variability, gene-environment interactions, polygenic interactions. These factors remain a challenge despite genome-wide association studies have identified multiple single nucleotide polymorphisms that are linked with lung cancer. Hence, future research studies must consider these challenges and should do research and try to improve in areas such as multi-ethnic genetic studies, should try to refine polygenic risk score, should functionally validate SNP to see whether they have any biological effect on lung cancer risk, should use SNPs to personalize prevention, diagnostic and treatment of lung cancer.

By now we know, most genetic studies related to lung cancer data are from European populations, therefore these data cannot be applied to other ethnic groups such as Asians, Africans (Amos et al.,2020). Hence, in future, the research must conduct on large scale multi ethnic groups to identify single nucleotide polymorphism that is specific to particular ethnic groups, thus prediction about genetic risk models could be improved (Wang et al.,2021). In addition, fine mapping techniques can be used to identify the exact SNP from ancestral linked variants that are actually linked with lung cancer. This technique improves precision in research and can be easily applied across different ethnic groups.

Polygenic risk score (PRS) is a tool that combines multiple SNPs to predict genetic predisposition related to lung cancer. However, this tool also has limitations and cannot be used in non-European populations because of differences in linkage disequilibrium and allele frequencies across different ethnic groups (Houlston et al.,2020). Therefore, future research should focus on developing a PRS tool that is specific to particular ethnic groups to improve accuracy of studies among different populations. As lung cancer risk is associated with both genetic and environmental factors, PRS should integrate both clinical risk factors and environmental factors to improve accuracy of the study. To increase PRS prediction model machine learning approaches should be done.

Most of the single nucleotide polymorphisms that are associated with lung cancer remain in the non-coding region, making it difficult to distinguish whether they directly affect genes or function through regulatory mechanisms i.e. altering gene expression (Zhao et al.,2019). Therefore, future research should focus on using gene editing tools like CRISPR-Cas9 to see how specific single nucleotide polymorphism (SNP) affects the expression of genes. Secondly, epigenetic studies should also be conducted as it affects gene expression. In lung cancer cells, some SNPs could activate or silence a gene, for example, a SNP that is related to lung cancer

risk, could increase DNA methylation in BRCA1 gene at the promoter region, thus its expression is prevented. Loss of BRCA1 gene expression prevents DNA repair in lung cells, thus increasing lung cancer risk. Thirdly, single cell sequencing on tumor cells should be carried out to determine which particular SNPs are responsible for tumor growth and which are neutral.

Genetic polymorphisms should be integrated into personalized medicine and these studies should be used in the prevention, diagnosis and treatment of lung cancer. The future direction for this is that genetic screening should be done for people who have high risk SNPs and PRS that could contribute to lung cancer risk, therefore, early detection is possible for these people. Pharmacogenomics studies should be conducted to personalize medicine that give benefits to individual patients. Moreover, some SNPs influence how genes interact with environmental exposures, such as carcinogens. Therefore, future research should focus on studying the interactions of SNPs with environmental exposures such as smoking and air pollution on lung cancer risk.

4.3 Clinical implications of genetic association studies related to lung cancer

Clinical implications of the genetic polymorphisms that are linked with lung cancer are applied to predict lung cancer risk, make personalized treatment approaches and are used in the prevention strategies for individuals who are at risk of developing lung cancer.

Several single nucleotide polymorphisms are linked with lung cancer risk such as genes XRCC1, ERCC1 which are involved DNA repair pathway, genes CYP2A6, GSTP1 which are involved in metabolism of carcinogens and gene CHRNA5 which drives nicotine addiction (Wang et al.,2021). Genes such as CHRNA5-A3-B4 are strongly associated with nicotine addiction, therefore, indirectly increasing the risk of developing lung cancer by driving the

individuals to smoke (Saccone et al.,2019). Hence, to predict the lung cancer risk, PRS tools can be used to identify individuals with SNPs that are associated with lung cancer risk. Thus, it allows for early screening for lung cancer risk.

Genetic polymorphism can be used in personalized treatment approaches which also helps to predict drug responses and minimize side effects. For example, individuals with higher PD-L1 gene variants tend to respond better to immune checkpoint inhibitors than those who have Low PD-L1 expression (Wang et al.,2021)

Polymorphisms such as CYP2A6 sometimes slows the breakdown of nicotine, and individuals with these polymorphisms become more addicted to smoking and can lead to higher risk of developing lung cancer (Saccone et al.,2019). Another gene GSTP1 which plays a role in removing harmful chemicals from the body, their polymorphisms sometimes make the body less effective at removing toxins and thus increasing susceptibility to lung cancer. If these higher risk genetic variants can be detected in particular individuals, then doctors could plan prevention strategies such as preventing individuals from heavy smoking or individuals with GSTP1 polymorphisms are screened more frequently who live in polluted environments.

Chapter 5

Conclusion

This review highlights the importance of genetic polymorphism that is associated with lung cancer risk. This has led to our understanding about the lung cancer disease susceptibility, its progression and treatment response and prevention strategies related to lung cancer. Various single nucleotide polymorphisms have been identified that are associated with lung cancer risk which include DNA repair genes polymorphisms such as BRCA2 rs11571833, RAD52 rs7963551 impaired DNA repair efficiency, leading to the accumulation of damaged DNA, thus increasing susceptibility to lung cancer. The BRCA2 mutations impair the homologous recombination repair mechanism, leading to increased accumulation of damaged DNA and thus increasing lung cancer risk. Likewise, the tumor suppressor gene TP63 polymorphisms such as rs10937405 are found to be associated with lung cancer in the East Asian population. Other DNA repair genes such as XRCC1 and ERCC1 and their polymorphisms influence platinum-based chemotherapy treatments outcomes. Detoxification genes involved in carcinogen metabolism such as GSTP1 and CYP2A6 regulate the process of removing harmful substances from the body. Polymorphism in CYP2A6 gene such as rs1801272 affects the metabolism of nicotine, hence influencing smoking behavior and lung cancer susceptibility. On the other hand, polymorphisms in detoxification genes such as GSTP1 modify the detoxifying efficiency in the body, thus impacting the air pollution and tobacco smoke on lung cancer risk. Nicotine addiction gene CHRNA5 and one of its polymorphisms such as rs16969969 reduces function of nicotinic acetylcholine receptors, thus increasing dependence on nicotine, which leads to increased exposure to carcinogens and increases mutations in lung cells. These metabolism related genes explain the importance of how interactions between gene and environment together influence lung cancer risk. Therefore, highlighting the need for prevention strategies

which include smoking cessation programs and screening programs for genetically higher risk individuals. Moreover, immune related single nucleotide polymorphism such as PD-L1 rs2297136 and rs4143815 influence PD-L1 expression which demonstrates the role of immunity in cancer development.

Association between genetic polymorphism and lung cancer also has some clinical applications where pharmacogenomics transforms lung cancer treatments into personalized treatment strategies. For example, EGFR inhibitors(gefitinib) can be used in people with EGFR polymorphisms. Furthermore, the success of platinum-based chemotherapy can be determined by how some genetic variants in metabolism and drug transport genes influence chemoresistance in lung cancer patients. Early detection of lung cancer and personalized treatment strategies can be done by the use of genetic screening techniques and polygenic risk score tools. In Spite of these advanced techniques, there are some limitations that make it difficult to transform genetic findings into clinical applications which include genetic heterogeneity among different ethnic groups, lack of replication of independent studies, the gene-environment interactions, small sample size, and statistical limitations. The polygenic risk score models which are used to predict lung cancer risk based on multiple single nucleotide polymorphism also lacks accuracy for non-European population because of linkage disequilibrium and allele frequency. In addition, many SNPs that are associated with lung cancer risk remain in non-coding region in the DNA, thus making it difficult determine their biological function. Thus, further improvements need to be done such as using CRISPR gene editing tool, single cell sequencing method and using epigenetic studies, the SNPs function could be validated.

To overcome these limitations, future research should focus on multi-omics approaches which include genetic, epigenetic, environment and transcriptomic data. More, multi ethnic studies

should be conducted, gene- environment interaction should be integrated into the genetic studies and PRS models should be refined, all of which will contribute in early detection, prevention strategies and personalized treatment approaches. The combination of pharmacogenomics, genetic screening and personalized treatment strategies will enhance early detection of lung cancer, increase chance of survival rate and will reduce unnecessary treatments, therefore, leading to more individualized management of lung cancer.

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